UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/602,934	06/24/2003	Baskaran Chandrasekar	201267.90011	1854

26710 7590 04/05/2006

QUARLES & BRADY LLP
411 E. WISCONSIN AVENUE
SUITE 2040
MILWAUKEE, WI 53202-4497

EXAMINER	
COTTON, ABIGAIL MANDA	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 04/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/602,934	CHANDRASEKAR ET AL.	
	Examiner	Art Unit	
	Abigail M. Cotton	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,10 and 15-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,10 and 15-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/25/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the amendment filed on January 25, 2006. Claims 9-10 and 15-33 are pending in the application, with claims 15-33 having been newly added.

Applicant's amendment to the priority section of the specification to recite the instant application as a continuation of the parent application 10/088,405, instead of a divisional, is approved.

The rejection of claims 9-14 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is withdrawn in view of Applicant's amendment to claim 9 to remove the phrase "by at least 50%" from the claim.

Applicant's arguments filed January 25, 2006 with regards to the rejection of the claims under 35 U.S.C. 103(a) have been fully considered but they are not persuasive.

The claims as newly amended and the newly presented claims are rejected as follows.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by the article entitled "17Beta-Estradiol Inhibits Proliferation and Migration of Human Vascular Smooth Muscle Cells: Similar Effects in Cells from Postmenopausal Females and Males" by Dai-Do et al, published 1996 (of record.)

Dai-Do et al. teaches that postmenopausal women receive estrogen replacement therapy, and that 17Beta-estradiol is believed to protect women against vascular disease (seepage 981, first full paragraph, in particular.) Dai-Do et al. teaches that studies with 17Beta-estradiol show that it inhibits growth-factor-induced SMC proliferation, which provides cardiovascular protective properties against restenosis (see abstract, in particular.) Dai-Do et al. also teaches that PTCA is associated with restenosis, and thus teaches that restenosis follows vascular injury caused by PTCA (see Introduction, in particular.) Thus, Dai-Do et al. teaches that a women (or man) receiving 17Beta-estradiol, for example via hormone replacement therapy, has reduced restenosis, such as restenosis that might otherwise occur after vascular injury caused by PTCA. Dai-Do et al. also teaches that local delivery of the hormone (e.g., after

percutaneous transluminal angioplasty to prevent restenosis) may be used also in male patients (see final full paragraph of page 984, in particular.) Accordingly, Dai Do et al. teaches that the 17beta-estradiol can be administered locally to prevent restenosis after PCTA, and thus is administered to a site in the lumen of a blood vessel that necessarily had been injured due to the implementation of the PCTA. Thus, Dai-Do et al. anticipates the methods of claims 1 and 24.

Claims 9-10, 18-19, 24 and 28-29 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,866,561 to Mark T. Ungs, issued February 2, 1999.

Ungs teaches a method for inducing angiogenesis in blood vessels proximal to stenosed regions, including application of an estrogen compound to the blood vessel walls at a treatment site proximal to or upstream of the stenosis (see abstract, in particular.) Ungs teaches that restenosis following PTCA is a signification problem, and that administration of estrogen to the stenosed, dilated region after PTCA has been suggested for the purposes of preventing restenosis (see column 1, lines 10-20 and 40-52, in particular), and thus teaches administration to an injured site, i.e. a vascular site that has been injured by PTCA. Ungs teaches that it is thus desirable to increase perfusion to heart tissue in place of or in addition to PTCA treatment (see column 1, lines 54-65, in particular.) Ungs teaches that a preferred method of treating stenosis involves application with a double walled drug delivery balloon catheter, as well as by coating a stent with an estrogen compound or by puncturing a vessel wall (see column

2, lines 5-45, in particular.) Ungs teaches that preferred estrogen compounds include 17-Beta estradiol (see column 4, lines 1-12, in particular), as in claims 9 and 24. Accordingly, Ungs teaches administration of 17-Beta estradiol in the lumen of a blood vessel having suffered vascular injury. Ungs furthermore teaches single administration of 17-Beta estradiol, as recited in claims 18 and 28, as Ungs teaches the compound can be administered via a stent or balloon catheter.

Regarding claim 10, Ungs teaches that the estrogen can be administered with an ionic carrier (see column 2, lines 32-40, in particular.)

Regarding claims 19 and 30, Ungs teaches the estrogens such as 17-beta estradiol can be administered with a drug delivery balloon catheter or on a stent, as discussed above, and thus teaches administering the compound with a device.

It is furthermore respectfully pointed out that the recitation "for reducing restensosis" in claim 9 has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *in re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152 88 USPQ 478, 481 (CCPA 1951.) Furthermore, it is noted that as Ungs teaches

administering the same compound via the same method as that instantly claimed, the method of Ungs would necessarily also reduce restenosis, as recited in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 22-23 and 32-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,866,561 to Mark T. Ungs, issued February 2, 1999.

Ungs is applied as discussed for claims 9, 18-19, 24 and 28-29 above, and teaches administration of 17-beta estradiol in the lumen of a blood vessel having suffered vascular injury.

Ungs does not specifically teach a specific embodiment in which the 17-beta estradiol is administered following percutaneous transluminal coronary angioplasty, as recited in claims 22 and 32, or simultaneously with percutaneous transluminal coronary angioplasty (PTCA), as recited in claims 23 and 33.

However, Ungs does teach that restenosis following PTCA is a significant problem (see column 1, lines 10-20, in particular), and teaches that treatment to increase perfusion to heart tissue, such as with estrogen compounds, are desirably performed in place of, or in addition to, PTCA (see column 1, lines 50-65, in particular.) Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the 17-beta estradiol following or simultaneously with the PTCA, based on the teachings of Ungs, with the expectation of increasing perfusion to heart tissue and for reducing the likelihood of restenosis.

Claims 15-17, 20-21, 25-27 and 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,866,561 to Mark T. Ungs, issued February 2, 1999, as applied to claims 9, 18-19, 22-23, 28-29 and 32-33 above, and further in view of U.S. Patent No. 5,512,557 to Peter Collins, issued April 30, 1996.

Ungs is applied as discussed above, and teaches administration of 17-Beta estradiol in the lumen of a blood vessel having suffered vascular injury. Furthermore, Ungs teaches administration of 17-Beta estradiol in the lumen of a blood vessel having suffered vascular injury, for example via catheter or a stent (see column 2, lines 5-45, in particular), as recited in claims 20-21 and 30-31.

Ungs does not specifically teach administration in the unit doses recited in claims 15-17 and 25-27. Ungs also does not specifically teach providing the compound in

combination with a pharmaceutically acceptable carrier on the stent or catheter, as recited in claims 20-21 and 30-31.

Collins teaches that 17-beta estradiol can be provided to treat coronary heart disease (see abstract, in particular.) Collins teaches that a suitable dose may be delivered in various forms, depending upon the route of administration, such as oral or parenteral administration (see column 2, lines 1-15, in particular) and the dosage may be varied according to the symptoms, age and body weight of the patient (see column 2, lines 15-25, in particular.) Collins teaches that a suitable daily dose may be from 0.5 mg to 2 mg (see column 2, lines 15-25.) Assuming administration of the dose to a female patient having a weight of about 65 Kg (~130 lbs), the dose is equivalent to a daily dose of about 8 micrograms/kg to about 30 micrograms/Kg, which meets and/or closely overlaps with the does ranges recited in the claims. Furthermore, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to optimize dose unit according to patient weight, means of administration, etc, in light of the teachings of Collins, to provide a desired dosage of the 17-B estradiol. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Collins et al. also teaches that 17beta-estradiol can be suitably formulated for administration with vehicles (carriers) that are commonly employed in the pharmaceutical arts (see column 2, lines 1-25, in particular.)

Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the dosage taught by Collins in the vascular injury treatment and estrogen delivery method of Ungs, because Collins teaches that the dose is capable of showing beneficial cardiovascular effects. Thus, one of ordinary skill in the art would have been motivated to deliver 17-beta estradiol by the method of Ungs and in the dosage of Collins, with the expectation of providing an effective dosage capable of yielding cardiovascular treatment.

One of ordinary skill in the art would furthermore have found it obvious to provide the vehicle of Collins et al. with the method of Ungs, because Ungs teaches administering 17beta-estradiol and Collins et al. teaches that 17beta-estradiol can be formulated with a pharmaceutically acceptable vehicle. Thus, one of ordinary skill in the art would have been motivated to provide a carrier with the 17beta-estradiol in the method of Ungs with the expectation of providing a suitable formulation for the administration of the 17beta-estradiol.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 9-10 and 15-33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 and 8-23 of copending Application No. 10/088,405, in view of U.S. Patent No. 5,866,561 to Ungs. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the co-pending application recite a method of using 17beta-estradiol or a derivative thereof to improve reendothelization and vascular endothelial function, by administering the compound at the injured site in the lumen of a blood vessel having suffered an injury, whereas the instant claims are to reducing

restenosis in a patient having suffered vascular injury by administering an effective dose of 17beta-estradiol or derivative at an injured site in the lumen of a blood vessel of the patient. Ungs teaches that agents that promote vascular endothelia growth can inhibit restenosis (see column 1, lines 30-40, in particular.) Accordingly, one of ordinary skill in the art would find it obvious to apply the reendothelization and vascular endothelial function improving method of the co-pending application for the reduction of restenosis, as in the instant claims, with the expectation that a method that improves the vascular endothelial growth and function would also inhibit restenosis.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicant's arguments filed January 25, 2006 regarding the rejection of the claims over the prior art have been fully considered but they are not persuasive.

In particular, Applicant's argue that Do-Dai et al. teaches in vitro inhibition of SMC proliferation, but does not teach the ability of the composition to reduce restenosis *in vivo*. Applicants further cite studies in the Kipshidze et al. article that they assert show promising *in vitro* results for drugs, specifically an antisense oligonucleotide targeting proliferating cell nuclear antigen and a bolus injection of phosphorotioate

oligomers, but that do not give good *in vivo* results for the inhibition of SMC proliferation. The Examiner notes that, nonetheless, Do-Dai teaches that 17beta-estradiol can be provided after PCTA treatment (and thus to an injured site) and is expected to inhibit restenosis, as discussed above. The Examiner furthermore notes that the lack of success with two compounds that are unrelated to those claimed would not teach one of ordinary skill in the art away from providing the 17beta-estradiol as claimed in the method as described by Do-Dai et al.

Applicants furthermore argue that Ungs does not teach the claimed method, because Applicants assert that Ungs does not teach (1) administration of 17-beta estradiol at the injured site of a vessel, and (2) administration of the compound for reducing restenosis.

The Examiner respectfully disagrees. Regarding point (1), Ungs teaches that restenosis following PTCA is a significant problem (see column 1, lines 15-20, in particular.) In other words, the site at which PTCA has been performed, which is necessarily a site at which injury has occurred, is the same site that is susceptible to restenosis. Ungs teaches that administration of estrogen to stenosed dilated region (i.e. the injured site) after PTCA has thus been suggested for the purposes of preventing restenosis (see column 1, lines 40-53, in particular.) While Ungs does teach that not all regions can be treated with PTCA, Ungs also teaches that it is also desirable to reduce the incidence of restenosis following PCTA or other procedures by providing the

estrogen compounds (see column 1, lines 50-65, in particular.) Thus, Ungs teaches administration of the estrogen compound to a site that is susceptible to restenosis, and that has or will experience injury due to techniques such as PTCA or other invasive techniques used to provide the estrogen compound to the stenosed region.

Regarding point (2), it is respectfully pointed out, as discussed above, that the recitation "for reducing restensosis" in claim 9 has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *in re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152 88 USPQ 478, 481 (CCPA 1951.) Furthermore, it is noted that as Ungs teaches administering the same compound via the same method as that instantly claimed, the method of Ungs would necessarily also reduce restenosis, as recited in the claim.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abigail M. Cotton whose telephone number is (571) 272-8779. The examiner can normally be reached on 9:30-6:00, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AMC

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER